IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: LEUNG *et al.*
Serial No.: 09/988,013
Filed: November 16, 2001
Title: IMMUNOCONJUGATES AND HUMANIZED ANTIBODIES SPECIFIC FOR B-CELL LYMPHOMA AND LEUKEMIA CELLS
Group Art Unit: 1643
Examiner: David Blanchard
Attorney Docket No.: IMMU:014US2
Confirmation No.: 7681

VIA EFS-WEB

REPLY BRIEF UNDER 37 CFR §41.41

COMMISSIONER FOR PATENTS
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Sir:

This reply appeal brief is being filed in accordance with the provisions of 37 C.F.R. § 41.41.

The facts and claims in the present case clearly are distinguishable from those in *University of Rochester v. G.D. Searle & Co., Inc.*

In the paragraph bridging pages 5 and 6 of the Answer, the examiner quotes from *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed. Cir. 2004):

> *Rochester* also attempts to distinguish *Fiers*, *Lilly*, and *Enzo* by suggesting that the holdings in those cases were limited to composition of matter claims, whereas the '850 patent is directed to a method. We agree with the district court that that is "a semantic distinction without a difference." *Univ. of Rochester*, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

However, the "method" in *Rochester* and the "method" in the present case are clearly distinguishable, as the following analysis will show.

At issue in *Rochester* were three independent claims and five dependent claims of US 6,048,850 ("the '850 patent"). The three independent claims read as follows:

1. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.

5. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the activity of the non-steroidal compound does not result in significant toxic side effects in the human host.

6. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the ability of the non-steroidal compound to selectively inhibit the activity of the PGHS-2 gene product is determined by:

a) contacting a genetically engineered cell that expresses human PGHS-2, and not human PGHS-1, with the compound for 30 minutes, and exposing the cell to a pre-determined-amount of arachidonic acid;

b) contacting a genetically engineered cell that expresses human PGHS-1, and not human PGHS-2, with the compound for 30 minutes, and exposing the cell to a pre-determined amount of arachidonic acid;

c) measuring the conversion of arachidonic acid to its prostaglandin metabolite; and

d) comparing the amount of the converted arachidonic acid converted by each cell exposed to the compound to the amount of the arachidonic acid converted by control cells that were not exposed to the compound, so that the compounds that inhibit PGHS-2 and not PGHS-1 activity are identified.

Thus, all of the claims in the patent in suit were directed to methods "for selectively inhibiting PGHS-2 activity in a human host" by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to [or in] a human host in need of such treatment." The claims were directed to methods of therapy in which the compound to be used in the therapy was defined in functional terms, *i.e.*, the ability to selectively inhibit activity of the PGHS-2 gene.

The examiner accurately defines the situation in *Rochester* vis-à-vis *Fiers*, *Lilly*, and *Enzo*, that is, "whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds." However, appellants here are not "lay[ing] claim" to either a "compound *per se*" or "a method…that entails the use of the compound." The claims in the present case are directed to a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody, and **not to a method of therapy** in which the compound used in the method of treatment is defined in functional terms.

The claims at issue here are more akin to those obtained in 1998 by the University of Rochester in US 5,837,479 ("the '479 patent"), which covered "a method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2)."[1] These claims are in distinct contrast to those in the '850 patent, the patent in suit in *Rochester*. The '850 patent covers ***methods of treatment*** ("a method for selectively inhibiting PGHS-2 activity in a human host"), and ***not methods "for identifying."***

The '850 patent was based on a divisional application of the application that gave rise to the '479 patent; hence the disclosure is identical. This disclosure did not include a single compound that was identified by the "method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2." However, the failure to disclose any compound has a different import with respect to a claim to a method for identifying a compound and a claim to a method of treatment using a compound identified according to this method. This was a key finding in *Rochester*, with the Federal Circuit making particular note of the district court's observation that "[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed **method of treatment**."[2]

Here the claimed method is not a "**method of treatment**" and therefore it is not impossible to practice the method according to the present invention without an identified compound. A skilled artisan can easily practice the method steps recited in claim 28, thereby to design humanized antibodies. Therefore, the present claims can be practiced without the disclosure of ***any*** compound. Again, the Board is invited to compare the situation presented by instant claims with

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[1] This patent was not included in the patent suit, and was not declared invalid.

[2] While *Rochester* cites *Enzo* as "as requiring a 'written description' of an invention separate from enablement," this passage emphasizes the relationship between the two, because whether "it is impossible to ***practice***" a claimed method is language clearly tied to ***enablement***, not written description.

that in the '479 and '850 patents. The current claims are much more like those in the '479 patent than in the '850 patent, which was the patent found to be invalid for lack of written description.

Moreover, the present case presents an example of a humanized antibody designed using the claimed method, hLL2. So even as to this point the present case is clearly distinguishable from the facts that led to a finding of invalidity for failure to provide a written description of the claims of the '850 patent. That is, while it is not necessary to disclose any compound designed by the presently claimed design method in order to satisfy either enablement or written description, it is noted that the present application goes beyond what is necessary and does exemplify design of a particular humanized antibody using the method according to the invention.

The written description requirement is tied in the *Rochester* case to the concept of notice to infringers. Thus, the Federal Circuit noted that "regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compound, or infringing methods from non-infringing methods." The "methods" in the latter part of this quote refers back to "methods that entail the ***use*** of a compound." Accordingly, the holding in *Rochester* does not apply to methods of identifying compounds as here.

In order to know whether there is infringement of a therapy claim, the Court is saying that a patentee must explicitly disclose at least one compound so that an infringer can tell whether he is infringing a therapy claim ("one critical aspect of the method — a compound that selectively inhibits PGHS-2 activity — was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound"). But in order to know whether there is infringement of a method of identifying or designing compounds, it is not necessary that any compound be disclosed, because an infringer can determine infringement merely by assessing whether the steps of the method are performed. In the second case, compounds are the end result of performing the method steps, whereas in the first case identification of the compound is one of the steps of the method, and is a step which must be performed before the step of treating the human host.

Viewed another way, had appellants included within the four corners of their specification a long laundry list of humanized antibodies produced by the presently claimed method, that listing would in no way have furthered the teaching of how to carry out the presently claimed method steps, or satisfied any notion of notice to infringers as alluded to in *Rochester*. Such a listing would be of no added benefit to an alleged infringer in assessing whether the present method steps had been infringed. The present claims satisfy the requirement of notice to infringers without such an

expanded listing of humanized antibodies. The size of the genus of antibodies that can be produced by the present method steps, or whether appellants have disclosed one or more than one member of this genus is immaterial to written description of the present method claims. As emphasized in appellant's brief:

> appellants here are not claiming a "genus" of humanized antibodies, of which hLL2 would be a species. ***Appellants are claiming a method,*** the implementation of which can be used to produce humanized antibodies.[3]

Later in the opinion, the Court returns to this infringement theme, citing *Reiffin v. Microsoft Corp.,* 214 F.3d 1342 (Fed.Cir.2000), for the proposition "that the purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not over-reach the scope of the inventor's contribution to the field of art as described in the patent specification,'" *Id.* at 1345. This ties in to a point made previously in appellants' brief, that

> The issue must always be approached from the perspective of what it *claimed*. What is claimed is a general method of designing amino acid sequences for humanized antibodies. The written description leaves no doubt that this method was in appellants' possession as of their earliest filing date.[4]

"Possession" goes hand in hand with "inventor's contribution to the art." Here, inventor's contribution is a method of designing humanized antibodies, and possession of this method is clearly conveyed by the present specification. By contrast, in *Rochester* the Court signaled that the University of Rochester was "over-reaching the scope of the inventor's contribution to the field of art described in the patent specification," when they attempted to use this disclosure of a ***method of identifying compounds*** to obtain ***claims to methods of therapy that would cover use of any compound so-identified where no compound was disclosed***. Appellants here are not over-reaching the scope of their contribution to the art.

The amendment of appellants' claims to recite selection of framework from particular antibodies does not imply universal or best fit frameworks that work with any CDRs.

After final rejection, appellants amended claim 28 to recite that the heavy chain FR4 is selected from the human NEWM antibody, the light chain framework regions are selected from the human REI antibody, and the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody. These selections correspond to those made when designing hLL2. It was thought that by making the selections in the independent claim correspond to those in the exemplified embodiment,

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[3] Brief at page 8, emphasis in original.
[4] Brief at bottom of page 10.

the examiner might be inclined to allow the claims without the necessity of an appeal. Moreover, these same selections have been made when appellants have humanized other antibodies, as detailed in the brief. In fact, as noted by the examiner, 4 of 10 antibodies in the table on page 12 of the brief use these selections.[5] However, appellants reiterate that they are not urging that there are universal or best fit frameworks that work with any CDRs. In any event, as noted by the examiner on page 14 of the Answer, the number of other antibodies that have been made with the selections as recited in current claim 28 is immaterial to the central issue in this case, which is whether there is "adequate written support in the instant application."[6] On this issue, the Board is referred back to the extensive discussion above and in the brief on appeal.

For these reasons and those stated in the brief on appeal, the Board is requested to reverse the decision of the examiner and pass the present case to issuance.

Respectfully submitted,

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AUGUST 4, 2008
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[5] In connection with claim 28 as amended, the examiner has noted that the two applications noted at the top of page 13 (US20030040606A1 and US20050033028A1) do not use the same selections. These applications did use the method of claim 28 as it was prior to amendment, but not the selections as now recited in claim 28.

[6] Answer at page 14, lines 10-13.